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Appendix S1

Development of the PSYCHS:

Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS

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Abstract

Aim: To harmonize two ascertainment and severity rating instruments commonly used for the clinical high risk syndrome for psychosis (CHR-P): the Structured Interview for Psychosis-risk Syndromes (SIPS) and the Comprehensive Assessment of At-Risk Mental States (CAARMS).

Methods: The initial workshop is described in the companion report from Addington et al. After the workshop, lead experts for each instrument continued harmonizing attenuated positive symptoms and criteria for psychosis and CHR-P through an intensive series of joint videoconferences.

Results: Full harmonization was achieved for attenuated positive symptom ratings and psychosis criteria, and partial harmonization for CHR-P criteria. The semi-structured interview, named Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS), generates CHR-P criteria and severity scores for both CAARMS and SIPS.

Conclusion: Using the PSYCHS for CHR-P ascertainment, conversion determination, and attenuated positive symptom severity rating will help in comparing findings across studies and in meta-analyses.

148 words

Key words: early detection, clinical high risk, ascertainment, severity rating, psychometrics

1 | INTRODUCTION

The clinical high-risk syndrome for psychosis (CHR-P), also known as the ultra-high risk (UHR) mental state, was first described 25 years ago (Yung et al, 1996) and has provided an influential paradigm for early detection and intervention in psychosis. CHR-P syndrome patients are youth and young adults who are symptomatic and impaired and also at risk for developing frankly psychotic disorders (Woods et al, 2021; Woods et al, 2001). The condition is listed in DSM-5 as Attenuated Psychosis Syndrome (American Psychiatric Association, 2022) as one of four specified “Other Specified Schizophrenia Spectrum and Other Psychotic Disorders” (ICD-10 F28) under the construct of “Conditions for Further Study”; further study has suggested substantial validity (Mensi et al, 2021; Salazar de Pablo et al, 2020). CHR-P syndromes are associated with a meta-analytic 20% probability of developing psychosis at two years, which increases over the long term peaking to 35% at 10-years (de Pablo et al, 2021b). Most CHR-P individuals who will not develop psychosis will continue displaying other poor mental health outcomes at follow-up (Addington et al, 2019; de Pablo et al, 2021a). Multiple biological markers predict onset of psychosis in CHR-P patients (Fusar-Poli et al, 2020), including recent evidence that thinning of cerebral cortex precedes and predicts psychosis (Collins et al, 2022). CHR-P a common, if under-recognized, condition, as evidenced by meta-analytic estimates of point prevalence in the general youth population (1.7%) and in the population of youth presenting for psychiatric care (19.2%) (Salazar de Pablo et al, 2021). A recent bibliographic analysis identified 1,637 unique research data publications, with two or more publications originating from 1,573 separate institutions in 49 countries (Lee et al, 2022). More than 100

specialty clinics for CHR-P have been organized in multiple countries across six continents (Kotlicka-Antczak et al, 2020).

Two semi-structured interviews have commonly been used to ascertain patients for CHR-P and to rate their severity of illness over time (Andreou et al, 2019; Daneault et al, 2013; Olsen and Rosenbaum, 2006): the Structured Interview for Psychosis-risk Syndromes (SIPS) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Miller et al, 1999; Yung et al., 1996). Psychometric properties for both instruments have been extensively studied, and predictive validity for these instruments has been excellent for the conversion to psychosis outcome (AUC=0.85) (Oliver et al, 2022). Interrater reliability (IRR) for CHR-P ascertainment has also been excellent, both for the SIPS (median kappa across 16 published samples 0.89) (Woods et al, 2019) and the CAARMS (median across three studies 0.845) (Fusar-Poli et al, 2012; Miyakoshi et al, 2009; Paterlini et al, 2019). IRR for attenuated positive symptoms has also been excellent for the SIPS (median ICC across 21 published samples 0.88) (Woods et al., 2019) and CAARMS (median ICC or Pearson r across eight studies 0.89) (Braham et al, 2014; Fusar-Poli et al., 2012; Lho et al, 2021; Miyakoshi et al., 2009; Paterlini et al., 2019; Wang et al, 2022; Yokusoglu et al, 2021; Yung et al, 2005).

Recently the US National Institute of Mental Health (NIMH) has spearheaded an effort to harmonize these two instruments (Addington et al, 2023). Harmonization was needed despite identical attenuated positive symptom content and general overall similarity (Schultze-Lutter et al, 2013) because of six important differences in: 1) organization of attenuated positive symptom content into items (Table 1), 2) scaling of items, 3) conceptualization of severity, 4) quantifying symptom frequency, 5) frank psychosis diagnosis criteria (Table 2), and 6) CHR-P syndrome criteria (Tables 3-5).

These six differences make it challenging if not impossible to translate severity scores or diagnoses from one instrument to another and consequently generate uncertainty about comparing findings from studies that use one but not the other (Addington et al., 2023). In fact, some authors have described the state of assessment in the CHR-P field as one of “near-Babylonian” confusion (Schultze-Lutter et al, 2011). Using both instruments in a single study has generally been impractical due to participant burden and cost considerations. Therefore harmonization seemed to be the only solution.

The goal of this effort was to create a new instrument that harmonizes the CAARMS and the SIPS to the degree feasible based on current knowledge. The harmonized instrument is called Positive SYmptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS). It generates fully harmonized positive symptom ratings, provides for scoring of all CAARMS and SIPS positive symptom items from a single interview, fully harmonizes psychosis criteria, and generates partially harmonized CHR/UHR diagnostic criteria for both the CAARMS and the SIPS. This paper describes the methods and results for the harmonization in detail, including limits to harmonization; it also briefly outlines our implementation in the ongoing Accelerating Medicines Partnership® Schizophrenia (AMP® SCZ) observational study (Brady et al, 2023).

2 | METHODS

2.1 | Harmonization process

The initial harmonization process began when the NIMH hosted a workshop on February 13th and 14th 2020, attended by 38 international participants and described in the companion report

(Addington et al., 2023). After the workshop, the lead experts for the SIPS and CAARMS (SWW and ARY) began a series of videoconference meetings in April 2020 facilitated by a NIMH program officer (SAW). These meetings considered workshop recommendations and unresolved issues and were generally held weekly for two hours. Beginning in January 2021, additional members with extensive practical experience with the CAARMS (SP, MJK) and the SIPS (BCW) joined these meetings.

Meeting time was spent reviewing the literature, comparing item content between SIPS version 5.6.1 (Keefe et al, 2021; Walsh, 2021) and CAARMS 2015 (Yung et al, 2015), ensuring that all attenuated positive symptom content in both instruments was captured in the PSYCHS by verbatim interviewer inquiries, reformulating the joint item content into new and distinct items (Table 1), ensuring the consistency of measurement concepts across items, harmonizing scaling, ensuring that the harmonized scale anchors for each item were distinct, ordered, and graded according to similar intervals within each measurement concept, and crafting interviewer and scoring instructions. All decisions were made by consensus, and minutes were taken by SAW.

2.2 | Limits to harmonization

The initial charge in the NIMH-hosted workshop was to fully harmonize the two instruments. The workshop ended with incomplete progress, however, due to the number and difficulty of the challenges presented. After more than a year of intensive weekly meetings, the working group members agreed that it was possible to fully harmonize the assessment of attenuated positive symptoms. It was also possible to fully harmonize the diagnostic criteria for frank psychosis used for excluding CHR-P at ascertainment and for determining conversion/transition to frank psychosis. Although some progress was made in harmonizing CHR-P syndrome criteria, in the

end, the different conceptualizations of the CHR-P syndrome proved too difficult to reconcile, and the group focused on designing the PSYCHS to generate data for both CAARMS and SIPS CHR-P syndrome criteria.

PSYCHS developers intended to keep the average administration time for the initial assessment version to no more than 90 minutes on average and no more than 60 minutes on average for the follow-up version, both broadly consistent with CAARMS and SIPS administration times. To meet these participant- and interviewer-burden goals, it was necessary to focus exclusively on diagnostic assessment and on attenuated positive symptoms that are required for that assessment. As a result, assessments for negative, disorganized, and general symptoms in the SIPS and for cognitive change, negative symptoms, behavioral change, motor/physical changes, and general psychopathology in the CAARMS were not included.

2.3 | Implementation process

Harmonization was completed by December 2021. Work then shifted to implementing the instrument in Research Electronic Data Capture (REDCap) and the in-house Research Project Management System (RPMS), in collaboration with three projects included in the AMP SCZ consortium: the Psychosis-risk Outcomes Network (ProNET; SWW, CEB, and JMK, PIs), the Trajectories and Predictors in the CHR for Psychosis Population: Prediction Scientific Global Consortium (PRESCIENT; BN and PJM, PIs), and the Psychosis Risk Evaluation, Data Integration and Computational Technologies (PREDICT) Data Processing, Analysis and Coordination Center (DPACC; MES and RSK, PIs).

Implementation of the initial assessment version in REDCap and RPMS was completed by May 2022. Rater training and certification then began, for which JA and AN joined the

working group meetings, and consensus calls were organized. Data collection for the initial assessment version began in the large observational study component of AMP SCZ in June 2022. Implementation of the follow-up version was completed by July 2022.

3 | RESULTS

Results are presented for the fully harmonized acquisition of attenuated positive symptoms, the fully harmonized psychosis determination, and the partially harmonized and parallel SIPS/CAARMS CHR/UHR determinations. Materials available and current use in AMP SCZ are also briefly described.

3.1 | Fully harmonized attenuated positive symptom acquisition

Full harmonization of the CAARMS and the SIPS attenuated positive symptoms was achieved in the areas of: symptom content, content organization into items, measurement concepts within each item, scaling of severity level, anchors for each level for each measurement concept for each item, fully-structured inquiries about patient health experiences mapping onto each item, and scoring of severity.

Figure 1 shows the conceptual framework underlying attenuated positive symptom acquisition in the PSYCHS. Following US Food and Drug Administration guidance (U.S. Department of Health and Human Services et al, 2022), the framework consists of a conceptual model and a measurement model. In the conceptual model, attenuated positive symptom-related health experiences resulting from CHR-P are organized into 15 distinct symptoms. Each of these is captured in the PSYCHS by two or more verbatim Inquiries and semi-structured Follow-up Questions. These health experiences are organized into three general concepts: 1) attenuated

delusions, 2) attenuated hallucinations, and 3) attenuated thought disorder. Together the three general concepts form the concept of interest (Overall Attenuated Positive Symptom Burden of the Clinical High Risk Syndrome for Psychosis). In the measurement model, the PSYCHS is a Clinical Outcomes Assessment (COA) instrument as defined by FDA (U.S. Department of Health and Human Services et al., 2022) and yields a CHR-P attenuated positive symptom severity index comprising severity scores from 15 measurement items corresponding to 15 health experience areas captured by the PSYCHS.

3.1.1 | Content coverage—Review of the separate instrument instructions, manuals, and positive symptom inquiries and items revealed identical positive symptom content across the SIPS and CAARMS.

3.1.2 | Content organization into items—Although positive symptom content was identical, the same content was organized across the SIPS and the CAARMS into different items and into a different number of items based on differing formulations of psychopathology. Table 1 shows how attenuated positive symptom content mapped across the instruments. For example, unusual somatic ideas were captured in P1 of the SIPS (Unusual Thought Content) because they were neither paranoid nor grandiose in nature and so did not belong in SIPS P2 or P3; the CAARMS, however, captured unusual somatic ideas in P2 (Non-Bizarre Ideas) because they were not bizarre in the sense that they were theoretically possible. Another example is grandiosity, which was considered an independent item in the SIPS (P3) but designated as a component of Non-Bizarre Ideas (P2) in the CAARMS. No procedure could be devised to harmonize the two instruments by reorganizing content into just a handful of items without losing the integrity of

individual items that have been strongly predictive of future psychosis in previous studies (Cannon et al, 2016). Thus Unusual Somatic Ideas, Ideas of Guilt, Jealous Ideas, and Unusual Religious Ideas each required separate items in the PSYCHS (Table 1 and Figure 1).

Since at least nine items would be needed to capture all of the CAARMS and SIPS attenuated positive symptom content, consideration was given to whether further splitting was desirable. Erotomania was separated from other forms of grandiosity, consistent with evidence that erotomania can constitute a distinct psychotic syndrome (Segal, 1989). Previously erotomania was rated in the SIPS under P3 grandiosity and in the CAARMS under P2 Non-Bizarre Ideas. We elected to divide the single perceptual abnormalities in both CAARMS and SIPS into six items: auditory, visual, olfactory, gustatory, tactile, and somatic, based on evidence that the combined perceptual abnormalities items predicted future psychosis poorly (Katsura et al, 2014; Perkins et al, 2015; Zhang et al, 2018) and mixed evidence that abnormalities of specific perceptual modalities may predict future psychosis differently (Ciarleglio et al, 2019; Lehembre-Shiah et al, 2017; Niles et al, 2019). Content of Disorganized Communication Expression was already harmonized (PSYCHS P15). Thus the PSYCHS was formulated with 15 attenuated positive symptom items (Table 1).

One experience, nihilistic ideas, had been captured in the CAARMS under P2 Non-Bizarre Ideas and in the SIPS under P1 Unusual Thought Content. We considered formulating nihilistic ideas into a separate item, perhaps along with perplexity and delusional mood, but in the end felt that additional psychopathology research was needed to properly construct a severity gradient and that for now nihilism should be placed within PSYCHS P1 (Unusual Thoughts and Experiences).

The name for P1 in both SIPS and CAARMS is Unusual Thought Content, and both instruments organize mental events and experiences such as thought insertion into this item. This organization is consistent with psychopathological classification of thought insertion as a delusion rather than a hallucination (American Psychiatric Association, 2013) due to the lack of a sensory component. Following Fish (Hamilton, 1984), who considered mental events such as thought insertion to be *experiences*, the name for PSYCHS P1 was changed to Unusual Thoughts and Experiences.

3.1.3 | Attenuated positive symptom measurement concepts—Positive symptom severity is complex and multidimensional, and symptom severity anchors in both SIPS and CAARMS have always contained mixtures of measurement concepts in the item anchors. Attention to distinguishing measurement concepts within the anchors has become more detailed and explicit with subsequent revisions for each instrument. With the revision from version 5.6 to 5.6.1 in 2017, SIPS anchors have been designed so that each item contains a graded description of each measurement concept for each severity level.

This structure was maintained in the PSYCHS. Each item is conceptualized as composed of, and each scale level for each symptom is closely anchored for, three or four measurement concepts: 1) symptom description (all items); 2) symptom tenacity (for attenuated delusion items P1 to P8), symptom source (for attenuated hallucination items P9 to P14), or symptom self-correction (for attenuated disorganized communication item P15); 3) distress due to the symptom (all items except P8 Grandiosity); and 4) interference (with other thoughts, feelings, social relations and/or behavior) due to the symptom (all items).

The measurement concepts are synthesized into a single rating for the item as follows: the

first two measurement concepts are co-primary and generally determine the item's single rating. For example, if an interviewer judges that symptom description matches anchor text for 5, and symptom tenacity/source/self-correction also matches anchor text for 5, the item single rating for that timeframe is 5.

The third and fourth measurement concepts (distress and interference) are secondary. In the example above, the secondary measurement concepts do not contribute to the single rating. The secondary measurement concepts only contribute to the single rating in the situation when the interviewer determines that the co-primary measurement concepts do not agree. For example, when the interviewer judges that symptom description matches anchor text for 4 but symptom tenacity/source/self-correction matches anchor text for 5, or vice-versa, the interviewer should take into account anchor text for distress due to the symptom and for interference due to the symptom. If *either* distress *or* impairment due to the symptom matches anchor text in the 5 or 6 range, the single rating for that item will be 5. If *both* distress *and* impairment due to the symptom match anchor text in the 4 or lower range, the single rating for that item will be 4.

Among the attenuated hallucinations items (P9-P14), the focus of the secondary measurement concept is on the perceived source of the perception, in other words the degree to which the experience is perceived to arise from a real source as opposed to arising from one's own thoughts. The concept of perceived source is derived from the CAARMS and represents a change for the SIPS. Previously the SIPS P4 Perceptual Abnormalities item considered the degree to which the sensory experience was believed to be real instead of the degree to which it was perceived as real. Colleagues occasionally pointed out the inconsistency in the SIPS in having a perceptual item rely on a delusional interpretation, and so the SIPS developers on the team were amenable to adopt the CAARMS procedure. Independent perceptual and delusional

items may facilitate research focusing on the co-occurrence and sequencing of onset of attenuated delusions and hallucinations (Mourgues et al, 2023; Smeets et al, 2015).

Thus the PSYCHS gives strong and often exclusive priority to the two primary measurement concepts in determining severity/intensity. The rationale for this approach was that distress or disability associated with attenuated positive symptoms may be affected by other factors in addition to actual attenuated positive symptom severity, such as depression or anxiety, consistent with a recent empirical analysis (Wilson et al, 2020).

3.1.4 | Harmonized attenuated positive symptom item scaling—Attenuated positive symptom item scaling differed between the CAARMS and SIPS. For the SIPS, the fully psychotic range was limited to level 6, the subsyndromal or CHR range was 3-5, and the non-pathological range was 0-2 for all five attenuated positive symptom items. For the CAARMS, the same was true for items P1 and P2, but for CAARMS P3 (perceptual abnormalities) the fully psychotic range was 5-6, the subsyndromal or CHR range was 3-4, and the non-pathological range was 0-2, while for CAARMS P4 (conceptual disorganization), the fully psychotic range was limited to level 6, the subsyndromal or CHR range was 4-5, and the non-pathological range was 0-3.

As part of the harmonization process, CAARMS developers felt that consistency across items was an advantage for raters, and anchor content for the PSYCHS was crafted so that the severity gradient reflected frank psychosis at level 6, the subsyndromal or CHR range at 3-5, and the non-pathological range at 0-2 for all 15 attenuated positive symptom items. On careful inspection of the original instrument anchors, it was possible to meld content from the two instruments so that, for example, level 6 on the PSYCHS attenuated hallucinations items retained

consistency with levels 5 and 6 from CAARMS P3 while also retaining consistency with the distinction between levels 5 and 6 on SIPS P4.

The labels for the anchor levels also differed slightly across the original instruments. For SIPS 5.6.1, levels 0-6 were labeled, respectively: Absent; Questionably Present; Mild; Moderate; Moderately Severe; Severe but not Psychotic; and Severe and Psychotic. For CAARMS 2015, levels 0-6 were labeled, respectively: Never, absent; Questionable; Mild; Moderate; Moderately severe; Severe; and Psychotic & severe. The working group agreed that these could be fully harmonized as: Absent; Questionable; Mild; Moderate; Marked; Severe but not Psychotic; and Psychotic and Very Severe.

3.1.5 | Harmonized attenuated positive symptom item anchors—Once the scaling challenges were surmounted, it was conceptually straightforward to meld text from the original instrument anchors into harmonized text for each measurement concept, for each anchor, and for each item. Careful attention was paid so that within each measurement concept for each item, the seven (0-6) levels described different severity levels of the same content, that the seven levels were each distinct from one another, that each adjacent level was ordered relative to its neighbors, and that a consistent increasing gradient of severity existed across levels within each measurement concept. The anchor sets for each item were further scrutinized for consistency with the anchor labels, such that, for example, the word “marked” was not used in an anchor under Severe but not Psychotic. Lastly, the anchors within each measurement concept were evaluated across items, so that, for example, the same words were not used for differing levels across items.

3.1.6 | Harmonized attenuated positive symptom inquiries—Since the CAARMS and the SIPS covered identical overall positive symptom content, harmonizing verbatim inquiries about participant’s health experiences was relatively straightforward. The two sets of inquiries were merged, and redundancies were eliminated.

3.1.7 | Concept of severity—The two instruments conceptualize severity similarly in most regards, as reviewed above, and when there is variability of severity within the measurement interval both instruments capture the highest severity during that interval. There is one important difference, however (Addington et al., 2023). The SIPS conceptualizes the synthesis of the measurement concepts for a particular item over the past month as *severity*. The CAARMS conceptualizes the same measurement concepts over the same recall interval as *intensity* rather than as severity and adds an additional severity measurement concept of symptom *frequency*. Intensity and frequency are then combined to yield CAARMS severity. Since this difference could not be harmonized, the PSYCHS generates ratings for both SIPS and CAARMS conceptualizations of severity. To acknowledge this difference, the synthesis of the four harmonized severity-relevant measurement concepts in the PSYCHS items (not including frequency) is termed *severity/intensity* within the instrument. In addition, a new severity score native to the PSYCHS is calculated as the sum of PSYCHS items P1-P15 (range 0-90).

3.1.8 | SIPS item generation and scoring of SIPS severity—For SIPS attenuated positive symptom severity, five items are generated from the PSYCHS, consistent with the mapping shown in Table 1. SIPS P1 severity is calculated as equal to the highest of PSYCHS items 1, 3, 4, 5, and 6 severity/intensity. SIPS P2 severity equals PSYCHS item 2. SIPS P3 severity is equal

to the higher of PSYCHS items 7 and 8. SIPS P4 severity is equal to the highest of PSYCHS items 9-14. SIPS P5 severity equals PSYCHS item 15. The SIPS total attenuated positive symptom severity score is the sum of SIPS items P1-P5 (range 0-30) as per usual practice.

3.1.9 | CAARMS item generation and scoring of CAARMS severity—The PSYCHS

incorporates the CAARMS 0-6 frequency ratings for each of the 15 items, with minor adjustments when rating the past month timeframe. Consistent with the mapping shown in Table 1 and with previous practice (Hartmann et al, 2020; Morrison et al, 2012), CAARMS P1 severity is equal to the product of PSYCHS P1 severity/intensity and frequency. CAARMS P2 severity is equal to the highest of the seven products of severity/intensity and frequency for PSYCHS items P2-P8. CAARMS P3 severity is equal to the highest of the six products of severity/intensity times frequency for PSYCHS items P9-14. The CAARMS total attenuated positive symptom severity score is the sum of the CAARMS P1-P4 severity/intensity-frequency products (range 0-144).

3.2 | Fully harmonized psychosis determination

CAARMS 2015 and SIPS 5.6.1 criteria for frank psychosis, used for excluding fully psychotic participants at study ascertainment and as criteria for conversion/transition to psychosis during study follow-up, differed in four of five domains, being identical only on the rating time frame (Table 2). Since conversion/transition was a frequently used outcome measure, the authors felt that it was essential to harmonize these criteria. Moreover, a study wherein both SIPS and CAARMS criteria were derived from a single modified CAARMS interview found considerable disagreement on presence of frank psychosis (Fusar-Poli et al, 2016b). The harmonization of

attenuated positive symptom severity (see above) permitted full agreement in the severity domain, and consensus was reached on the remaining three domains, as described in sections 3.2.1 and 3.2.2. The fully-harmonized psychosis criteria are included in Appendix S1.

3.2.1 | Harmonization of duration and frequency criteria for frank psychosis—The SIPS has required a duration of fully psychotic symptoms of one month to qualify for psychotic disorder, consistent with DSM-5 criteria for schizophrenia (American Psychiatric Association, 2022). CAARMS duration criteria were greater than or equal to one week. In practice the SIPS duration and frequency criteria could permit a frank psychosis determination in as little as 16 days if the psychotic-level symptoms were experienced daily (which averages to four days a week for a month). However, practitioners and patients and their families were often reluctant to wait that long to institute treatment for frank psychosis, and the SIPS developers were agreeable to adopt the CAARMS frequency and duration criteria (Table 2).

3.2.2 | Harmonization of the frank psychosis dangerousness criterion—The SIPS waiver of frequency and duration criteria when fully psychotic symptoms were disorganizing or dangerous had been a sticking point in the initial NIMH workshop (Addington et al., 2023). This waiver was meant in part to mitigate the risk of delayed SIPS diagnosis of psychosis due to the one month duration criterion when the need for treatment was immediate. The shorter CAARMS duration requirement, and its exception for cases that received new or increased antipsychotic medication, mitigated the risks associated with the longer SIPS duration criteria to some extent. However, those risks were not mitigated entirely. In addition, the SIPS waiver of the frequency and duration criteria when fully psychotic symptoms were disorganizing or dangerous also

functioned to mitigate a difficulty with the duration criteria when evaluating a person shortly after onset and when frank psychosis was clear-cut. This difficulty is that clinicians and researchers can be left in limbo without a psychosis determination if the participant is unable to be reevaluated a week later. That situation can occur around the time of conversion/transition if frank psychosis leads the participant to disengage from a clinical service or to be unable or unwilling to continue research participation. The SIPS waiver of the frequency and duration criteria resolves this difficulty in cases where symptoms are so clearly indicative of frank psychosis that they are associated with danger to self or others.

During the course of the intensive follow-up meetings, the CAARMS developers found these arguments reasonably compelling and were agreeable to adopt the SIPS waiver, so long as the phrase “seriously disorganizing or dangerous” was reworded. SIPS developers had on occasion been asked questions about what “seriously disorganizing” meant, or needed to correct confusion between “disorganizing” and disorganization symptoms, and thus the authors agreed on substituting “imminently dangerous, physically or to personal dignity or to social/family networks.” These criteria enable a psychosis diagnosis to be made at a single visit when, for example, a person’s dignity and reputation are threatened by psychotic behavior or when their or another’s life is endangered due to psychotic thinking or behavior.

3.3 | Partially harmonized and parallel CHR/UHR determination

Following the CAARMS, the SIPS has always generated three CHR/UHR syndromes based on the same three principles: 1) presence of attenuated positive symptoms (CAARMS Attenuated Positive Symptom Intensity and Attenuated Positive Symptom Frequency/SIPS Attenuated Positive Symptoms Syndrome, Table 3), 2) presence of brief fully psychotic symptoms

(CAARMS Brief Limited Intermittent Psychotic Symptoms/SIPS Brief Intermittent Psychosis Syndrome, Table 4), and 3) presence of trait vulnerability and functional decline (CAARMS Vulnerability group/SIPS Genetic Risk and Functional Deterioration, Table 5). The detailed definitions for each of the three CHR/UHR syndromes differed, however. In the end the working group was able to reconcile these differences only to a relatively minor degree (sections 3.3.1 and 3.3.2).

For the syndromes based on presence of attenuated positive symptoms (Table 3), the achievement of symptom severity harmonization offered promise, and the frequency criteria could potentially have been harmonized, but neither investigator group could compromise on the several remaining differences. The SIPS required attenuated positive symptoms to have been present in the past month and considered them in remission if they were no longer present in the past month (Woods et al, 2014), while the CAARMS permitted attenuated positive symptoms to have been present at any time in the past year. A compromise period of six months was proposed at the workshop (Addington et al., 2023), but during the extended discussions SIPS developers could not agree that symptoms no longer present in the past month should not be considered in at least partial remission. Moreover, the SIPS requires one or more attenuated positive symptoms to have begun or worsened in the past year, while the CAARMS does not. SIPS developers considered that epidemiologic (Schultze-Lutter et al, 2014) and other (Addington et al., 2023; Brucato et al, 2019; Woods et al., 2014) evidence suggested that the worsening criterion favorably excluded large numbers of patients who were no longer at high risk of conversion/transition, while CAARMS developers considered that the SIPS unfavorably excluded large numbers of patients with a need for treatment.

Lastly, the SIPS developers preferred accordance with the DSM-5 principle of parsimony such that a second diagnosis is not needed if all of its features are accounted for by another disorder, whereas the CAARMS was often employed on its own in a clinical context and so CAARMS developers were concerned that excluding patients from a CAARMS grouping could cause them to be excluded from care. Unable to agree, the authors settled for requiring the PSYCHS to include questions that would generate both sets of CHR/UHR criteria.

The issues preventing full harmonization for the syndromes based on presence of brief fully psychotic symptoms (Table 4) were similar, as were the issues preventing full harmonization for the syndromes based on trait vulnerability and functional decline (Table 5).

3.3.1 | Modifications to CAARMS UHR criteria—CAARMS developers agreed to remove functioning criteria based on the Social and Occupational Functioning Assessment Scale (SOFAS) (Morosini et al, 2000) from the symptom-based UHR syndromes (Tables 3 and 4), harmonizing with the SIPS. These criteria were removed as it was acknowledged that (1) treatment of UHR individuals may be needed in the absence of functional decline and (2) removing the functional decline criterion would enable early intervention to prevent deterioration. At the initial NIMH workshop (Addington et al., 2023), the consensus had been that the field should abandon the CAARMS Vulnerability group/SIPS Genetic Risk and Deterioration subtype due to evidence that it was infrequent, especially in the absence of other subtypes, and did not predict onset of psychosis (Fusar-Poli et al, 2016a). AMP SCZ investigators, however, saw value in the subtype for the study of functional outcomes, leading to its retention. CAARMS developers agreed to base the Vulnerability group criteria on current or past schizotypal personality disorder (SPD) (First, 2014) rather than solely on current SPD

(Table 5) after reviewing evidence that the diagnostic stability of SPD is not fully trait-like (Grilo et al, 2004). The modified CAARMS UHR criteria are included in Appendix S1.

3.3.2 | Modifications to SIPS CHR criteria—The SIPS has based the functional assessment requirement for Genetic Risk and Deterioration (GRD, Table 5) on the Global Assessment of Functioning (GAF) (Hall, 1995). Because of observations that GAF assessment of functioning was confounded by symptom severity (American Psychiatric Association, 1994), SIPS developers agreed to replace the GAF with the SOFAS, thus harmonizing the functional assessment scale with the CAARMS Vulnerability grouping. The modified SIPS GRD criteria are included in Appendix S1.

3.4 | Available materials

The Interviewer Manual, training and certification materials, the Screening Instrument for ascertainment and initial severity rating, and the Follow-Up Instrument for serial rating of severity, conversion/transition, and remission, are freely available for use by the research community and will become accessible on the AMP SCZ website, developed by the PREDICT DPACC in collaboration with members of ProNET and PRESCIENT with input from NIMH staff: <https://www.ampscz.org>. Data sharing is otherwise not applicable to this article as no datasets were generated or analyzed for the current article.

The PSYCHS will be available in an on-line REDCap version and as a printable paper copy. The on-line version adaptively skips questions made unnecessary by previous interviewer entries, provides just-in-time guidance only when needed, and automatically conducts calculations for determining psychosis and CHR/UHR criteria. Information required at follow-up

to determine new onset of psychosis or CHR-P syndromes is pulled automatically from previous visits. The coding of the calculations and branching logic for the PSYCHS in REDCap was carried out by members of PREDICT DPACC and ProNET, with testing across ProNET and PRESCIENT.

3.5 | Current use

The PSYCHS is currently in use in the 42-site AMP SCZ (Brady et al., 2023) observational study (<https://www.ampscz.org>). As of December 2022, more than 100 interviewers had been trained and certified, more than 100 participants had undergone assessment with the Screening Instrument, and five coordinated weekly consensus calls were ongoing. All persons gave their informed consent prior to their inclusion in the study.

4 | DISCUSSION

The principal finding of the present report is that it has been possible to harmonize the two most widely-used instruments for diagnosis and severity rating in individuals at clinical high risk for psychosis into one instrument, the PSYCHS. Full harmonization was achieved for attenuated positive symptom ratings and for psychosis diagnostic criteria, and the instrument generates partially harmonized CHR/UHR diagnostic criteria for both CAARMS and SIPS as well as severity scores for both CAARMS and SIPS.

The PSYCHS can be used instead of individual SIPS or CAARMS assessment for CHR-P ascertainment and attenuated positive symptom severity rating. When used in this way, future studies ideally would permit inclusion of participants who meet criteria for either CAARMS

UHR or SIPS CHR Progression, and sensitivity analyses in a data supplement could then report whether findings differed by CAARMS vs SIPS ascertainment or when employing CAARMS vs SIPS severity ratings. This practice would be helpful in comparing findings across studies and with meta-analysis.

4.1 | Strengths

The primary strengths of the PSYCHS are: 1) it harmonizes two instruments which both possess excellent psychometric properties, 2) the harmonization was conducted with great care by experts in both instruments, and 3) the attenuated positive symptom anchors provide detailed guidance for each of the 15 attenuated positive symptoms and are harmonized with particular attention to ensuring that anchors for each item are distinct, ordered, and graded according to similar intervals within each measurement concept. These changes are expected to yield even higher interrater reliability than already achieved with the original instruments and therefore improved signal detection. The on-line versions adaptively minimize administration time, missing data, and arithmetic errors.

4.2 | Limitations

There are also a number of limitations to the PSYCHS in its current stage of development. First and foremost is the inability of the authors to fully harmonize the CHR-P diagnostic criteria. One of the difficulties is due to the limited evidence base available to contribute to deliberations. We are aware of only one study that reports conducting independent CAARMS and SIPS interviews in the same CHR participants (Kwon et al, 2012), and the report does not present diagnostic agreement or comparative predictive validity analyses. A recent study in relatives of patients

with schizophrenia, however, also conducted independent interviews and reported 93% agreement, but agreement was largely due to the low prevalence of CHR in the sample of relatives. Of 17 cases diagnosed as CHR by either interview, the two interviews agreed on only 5 (29%) (Wang et al., 2022). Methods that rely on conducting only one interview and then estimating whether participants meet criteria for the other interview, while understandable in terms of limiting participant burden, may not be able to capture the other interview's assessment accurately, given the differences in the details of the data collection required. Use of the PSYCHS in the AMP SCZ sample should enable analyses of diagnostic agreement between, and comparative predictive validity of, SIPS and CAARMS CHR criteria in a large sample of the same subjects. Based on these data it may be possible to fully harmonize the CAARMS and the SIPS CHR criteria in the future.

A second limitation derives from the PSYCHS being a new instrument whose psychometric properties need to be established. While interrater reliability has been excellent (section 1) for both the CAARMS and the SIPS, similarly excellent inter-rater reliability for the harmonized PSYCHS cannot be assumed. We will conduct reliability studies as part of the AMP SCZ observational study, as well criterion validity (Sheehan et al, 1998) and other psychometric studies, in accordance with guidelines from the US Food and Drug Administration (U.S. Department of Health and Human Services et al., 2022).

A third limitation is the synthesis of a single severity rating for each item across up to four measurement concepts. While the single severity rating has always been used for the SIPS and the CAARMS and could be considered a strength for assessment of outcomes, independent rating of each measurement concept may provide sufficient added value for the purposes of predicting outcome to offset the additional burden on participant and interviewer. For example,

there is mixed evidence as to whether distress due to attenuated positive symptoms predicts future onset of frank psychosis independently from symptom severity (Nelson et al, 2022; Power et al, 2016; Pratt et al, in press; Rapado-Castro et al, 2015; Rekhi et al, 2019). We plan to investigate the independent rating of each measurement concept within AMP SCZ. Regarding the synthesis of measurement concepts by the interviewers, a cognitive debriefing study may be needed to demonstrate whether interviewers understand the method of synthesis.

Lastly, the PSYCHS contains 15 separate attenuated positive symptom items. While early experience in AMP SCZ indicates that administration times generally correspond to the intended 60-90 minutes, there have been exceptions, especially for an individual interviewer's first case or two as they gain familiarity with navigating the instrument in REDCap or RPMS. Analyses from AMP SCZ will be used to determine whether certain items could be consolidated. The increased focus on positive symptoms also has required that negative, disorganized, and general symptoms must be rated using separate scales. When used to make CAARMS Vulnerability grouping/SIPS GRD determinations, the PSYCHS relies on the SOFAS (Morosini et al., 2000) for functional assessment, as well as on the Structured Clinical Interview for DSM-5 Personality Disorders (First, 2014) and the Family Interview for Genetics Studies (Maxwell, 1992) for determining presence of schizotypal personality disorder and first-degree family history of psychosis, respectively.

4.3 | Summary

The Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS semi-structured interview (PSYCHS) has been developed to harmonize the two most widely-used instruments for diagnosis and severity rating in patients at clinical high risk for psychosis

(CHR-P). Use of the PSYCHS should facilitate comparing findings across studies in the CHR-P field.

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Table 1. Content Comparison across SIPS, CAARMS, and PSYCHS items

PSYCHS Item	SIPS Item	CAARMS Item
P1 Unusual Thoughts and Experiences	P1 Unusual Thought Content	P1 Unusual Thought Content
P2 Suspiciousness/Paranoia	P2 Suspiciousness	P2 Non-Bizarre Ideas
P3 Unusual Somatic Ideas	P1 Unusual Thought Content	P2 Non-Bizarre Ideas
P4 Ideas of Guilt	P1 Unusual Thought Content	P2 Non-Bizarre Ideas
P5 Jealous Ideas	P1 Unusual Thought Content	P2 Non-Bizarre Ideas
P6 Unusual Religious Ideas	P1 Unusual Thought Content	P2 Non-Bizarre Ideas
P7 Erotomantic Ideas	P3 Grandiose Ideas	P2 Non-Bizarre Ideas
P8 Grandiosity	P3 Grandiose Ideas	P2 Non-Bizarre Ideas
P9 Auditory Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P10 Visual Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P11 Olfactory Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P12 Gustatory Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P13 Tactile Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P14 Somatic Perceptual Abnormalities	P4 Perceptual Abnormalities	P3 Perceptual Abnormalities
P15 Disorganized Communication	P5 Disorganized Communication	P4 Disorganised Speech

Green text indicates the same health experience content is contained in the same item in SIPS 5.6.1 and CAARMS 2015; red text indicates the same health experience content is contained in different items in SIPS 5.6.1 and CAARMS 2015.

Table 2. Frank psychosis criteria for the SIPS and the CAARMS and the harmonized PSYCHS criteria

	Psychosis Criteria		
Instrument	SIPS 5.6.1	CAARMS 2015	PSYCHS
Severity	Any of SIPS P1-P5=6	Any of CAARMS P1-P4=6, or P3=5	Any of PSYCHS P1-P15=6
Timeframe	Lifetime	Lifetime	Lifetime
Frequency	One hour per day or more at an average frequency of four days a week	3 or more days a week - one hour or more a day, or at least daily	3 or more days a week - one hour or more a day, or at least daily
Duration	One month	One week or longer unless new or increased antipsychotic	One week or longer unless new or increased antipsychotic
Danger	Frequency and duration waived if seriously disorganizing or dangerous	None	Frequency and duration waived if imminently dangerous*

* physically or to personal dignity or to social/family networks

Red text indicates differences between SIPS and CAARMS, green text indicated harmonized criteria for psychosis

Table 3. PSYCHS CHR-P criteria based on attenuated positive symptoms

Original Instrument	SIPS 5.6.1	CAARMS 2015
Criteria	Current APSS Progression	Attenuated Positive Symptom Intensity
Severity	Any positive symptom scored 3-5	Any positive symptom scored 3-5
Timeframe	Past month	Past twelve months
Attribution	At least one symptom scored 3-5 is <i>not</i> explained better by another DSM disorder	At least one symptom scored 3-5 occurred outside of peak intoxication from a substance known to be associated with psychotic experiences (e.g. hallucinogens, amphetamines, cocaine)
Frequency	At least one symptom also occurred on average \geq once/week	At least one symptom also occurred one or more days a month - more than one hour a day or 3 or more days a week
Worsening	At least one symptom also began or worsened in the past year	None
Functional Change	None	$\geq 30\%$ drop in the SOFAS , sustained ≥ 1 month, within the past year, relative to premorbid level
or Functional Deficit	None	or SOFAS of 50 or less for past 12 months or longer
Criteria	None	Attenuated Positive Symptom Frequency
Severity	None	Any positive symptom scored 6
Timeframe	None	Past twelve months
Frequency	None	At least one symptom occurred one day a month but less than two days - more than one hour a day or 3 or more but less than 7 days a week
Functional Change	None	$\geq 30\%$ drop in the SOFAS , sustained ≥ 1 month, within the past year, relative to premorbid level
or Functional Deficit	None	or SOFAS of 50 or less for past 12 months or longer
Current Statuses	Also provides criteria for Lifetime, Persistence and Partial and Full Remission	None

Green text indicates revised from original instrument with strike-through indicating its removal, red text indicates differences between SIPS and CAARMS remaining in the PSYCHS

APSS= Attenuated Positive Symptom Syndrome

Table 4. PSYCHS CHR-P criteria based on brief fully psychotic symptoms

Original Instrument	SIPS 5.6.1	CAARMS 2015
Criteria	Current BIPS Progression	Brief Limited Intermittent Psychotic Symptoms (BLIPS)
Severity	Any positive symptom scored 6	Any positive symptom scored 6
Timeframe	Past month	Past twelve months
Attribution	At least one symptom scored 6 is <i>not</i> explained better by another DSM disorder	At least one symptom scored 6 occurred outside of peak intoxication from a substance known to be associated with psychotic experiences (e.g. hallucinogens, amphetamines, cocaine)
Frequency	At least one symptom also occurred \geq several minutes a day at least once in the past month	At least one symptom also occurred three or more days a week - more than one hour a day or at least daily
Duration	None	Less than one week
Worsening	At least one symptom also began or worsened in the past three months	None
Functional Change	None	$\geq 30\%$ drop in the SOFAS, sustained ≥ 1 month, within the past year, relative to premorbid level
or Functional Deficit	None	or SOFAS of 50 or less for past 12 months or longer
Current Statuses	Also has criteria for Lifetime, Persistence and Partial and Full Remission	None

Green text indicates revised from original instrument with strike-through indicating its removal, red text indicates differences between SIPS and CAARMS remaining in the PSYCHS

BIPS=Brief Intermittent Psychosis Syndrome

BLIPS=Brief Limited Intermittent Psychotic Symptoms

Table 5. PSYCHS CHR-P criteria based on trait vulnerability and functional impairment

Original Instrument	SIPS 5.6.1	CAARMS 2015
Criteria	Current GRD Progression	Vulnerability group
Family Hx	Psychosis in first degree relative	Psychosis in first degree relative
or Schizotypy	Current or past SPD in participant	Current or past SPD in participant
Timeframe	Past month	Past year
Functional Change	≥ 30% drop in the SOFAS, over the past month, relative to 12 months prior	≥ 30% drop in the SOFAS, sustained ≥ 1 month, within the past year, relative to premorbid level
or Functional Deficit	None	or SOFAS of 50 or less for past 12 months or longer
Current Statuses	Also contains criteria for Lifetime, Persistence and Partial and Full Remission	None

Green text indicates revised from original instrument, red text indicates differences between SIPS and CAARMS remaining in the PSYCHS

GRD=Genetic Risk and Deterioration

SOFAS=Social and Occupational Functioning Assessment Scale

Figure legend

Figure 1. COA[†] conceptual framework for the PSYCHS[‡] symptom severity assessment. The conceptual framework consists of a conceptual model (left side of panel) and a measurement model (right side of panel). In the conceptual model, attenuated positive symptom-related health experiences resulting from the Clinical High Risk Syndrome for Psychosis are organized into 15 distinct symptoms. These health experiences are organized into three general concepts: 1) attenuated delusions, 2) attenuated hallucinations, and 3) attenuated thought disorder. Together the three general concepts form the concept of interest. In the measurement model, 15 measurement items corresponding to the health experience areas captured by the PSYCHS yield severity scores that in turn are used to compute a Clinical High Risk Syndrome for Psychosis severity index.

† Clinical Outcomes Assessment

‡ Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS

